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WHITEMAN,B	
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Please find below and/or attached an Office communication concerning this application or proceeding.

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PTO-90C (Rev. 2/95)

*U.S. GPO: 2000-473-000/44602

Office Action Summary	Application No. 09/610,313	Applicant(s) BARNETT ET AL.	
	Examiner Brian Whiteman	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-40 and 42-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Priority

Priority to 09/475,704 filed on 12/30/99, 60/114,495 filed 12/31/99, and 60/152,195 filed on 9/1/99 are acknowledged. However, SEQ ID NOs: 30-32 do not appear to be present in any of the prior applications that the applicants are claiming priority to.

Information Disclosure Statement

The information disclosure statement filed on August 20, 2001 does not fully comply with the requirements of 37 CFR 1.98 because: applicant misspelled an author's name in the citation of a journal article listed on the 1449.

The examiner has considered all references, but in order to have the journal article with the correct spelling of the author initialed and dated on the 1449, a new 1449 properly citing the journal article must be filed with the response to this office action. Failure to comply with this notice will result in the above mentioned information disclosure statement being placed in the application file with the non-complying information **not** being considered. See 37 CFR 1.97(i).

Response to applicants' traverse to restriction requirement.

Applicants' traverse that: 1) Groups I through III are all classified in class 435, subclass 320.1 and class 514, subclass 44; Groups IV-VI are all classified in class 435, subclass 70.1, class 514, subclass 2 and would not be an undue burden on the examiner to search all groups. 2) Applicants submit restriction requirement to redefine and combine Groups I to VI, drawn to polynucleotides Pol polypeptides and compositions comprising these polynucleotide sequences. See paper no. 7, pages 2-3.

Applicants' traversal on the grounds encompassing issues 1-2 is found partially persuasive. First, the restriction between Groups I-VI is withdrawn and will be rejoined. Groups I-III will be considered **Group I** (*e.g.* 1-40 and 42-47); **Group II** will encompass claim 41. Second, the traversal is not found persuasive because each of the inventions I and II require a separate search status on the basis of the classification system, which recites an enormous number of potential and patentably distinct inventions within each class and subclass. In addition, each distinct invention would require a different search for the following reasons: The elected invention is drawn to an expression cassette comprising an HIV Pol polypeptide. Group II is a method of polypeptide therapy that has a different function and effect compared to the effect of Group I. Furthermore, Group I can be used in a materially different process than the process in Group I as shown in the process of Group II. Therefore, while the search for each invention may overlap there is no reason to believe that they are coexistent. Because these inventions are distinct for the reasons given above and the literature search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper.

Thus, the requirement is deemed proper.

Upon further consideration, the species election requirement and subdivided in paper no. 7, pages 8-9, into separate groups based on cells has been withdrawn due to the novelty of the expression cassette comprising an HIV Pol polypeptide.

Claim 41 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Election was made with traverse in Paper No. 7.

Claims 1-40 and 42-47, to which the following grounds of rejection are applicable, are pending.

Claim Objections

Claim 1 is objected to because of the term "including". In view of compact prosecution, the term "including" will be read as comprising.

Claim 36 should read, "wherein said composition is delivered by using a particulate carrier."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 4, as best understood, is readable on a genus of viral cytokines, wherein the genus of viral cytokines is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates production of an expression cassette comprising a polynucleotide encoding an HIV Pol polypeptide and further comprising one or more nucleic

acids encoding one or more viral cytokines. The specification does not provide sufficient guidance for production of an expression cassette comprising a polynucleotide sequence encoding an HIV Pol polypeptide and one or more nucleic acids encoding one or more viral cytokines

However, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of expression cassettes comprising a polynucleotide sequence encoding an HIV Pol polypeptide and further comprising one or more nucleic acids encoding one or more viral cytokines and/or a genus of viral cytokines as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of viral cytokines that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to a genus of viral cytokines. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming unspecified viral cytokines and/or a genus of an expression cassette comprising a polynucleotide encoding an HIV Pol polypeptide and further comprising one or more nucleic acids encoding one or more viral cytokines that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v.*

Revel, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of the claimed viral cytokines and/or an expression cassette comprising a polynucleotide sequence encoding Pol polypeptide and further comprising one or more nucleic acids encoding one or more viral cytokines that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1-40 and 42-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) An expression cassette comprising a polynucleotide sequence encoding a Pol polypeptide, wherein the polynucleotide sequence encoding said Pol polypeptide is set forth in SEQ ID NOs: 30-32; 2) The expression cassette of 1, wherein said polynucleotide sequence further comprises a nucleic acid sequence encoding a viral polypeptide selected from Gag, Env, vif, vpr, tat, rev, vpu, nef, and combinations thereof; 3) A composition for generating an immunological response in a mammal, comprising the expression cassette of 1; 4) A method for generating an immune response in a mammal, comprising intramuscularly

administrating the expression cassette of 1 to said mammal, and does not reasonably provide enablement for the rest of the disclosure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possession of a genus of viral cytokines), particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended.

The invention lies in the field of producing an immunogenic composition or vaccine using an expression cassette comprising an HIV Pol polypeptide set forth in SEQ ID NOs: 30-32.

The state of the art exemplified by Gurunathan et al. indicates that the goal of developing effective vaccines for a particular disease depends on several factors:

1) Identification of a conserved antigen capable of inducing protection is an outbred population.

2) Design vaccines that can induce an appropriate qualitative and quantitative immune response.

3) Some diseases require different types of immune responses for effective primary and memory immunity (*J Immunol*, Vol. 161(9), pg. 4563, November 1998).

In addition, major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered

2) The route and time course of administration, the sites of administration, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of

mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

3) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method (Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998).

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the subject being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson indicates that the state of the art before 1998, and teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in a subject is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma et al., *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). Thus, in view of the state of the art, producing an immunogenic composition or vaccine using a replicant defective vector encoding a nucleotide sequence is considered unpredictable.

The application contemplates: 1) Expression assays for the synthetic coding region of Pol, Env, and Gag-protease expression cassettes; 2) In vivo immunogenicity of Gag, Pol, and Env expression cassettes using plasmid DNA carrying the synthetic Gag, Pol, and Env expression cassette; 3) DNA immunization of non-human primates by administering intradermally, mucosally, bilaterally, intramuscularly into the quadriceps using various doses of a synthetic Pol, Env, and Gag-containing plasmid; 4) In vitro expression of recombinant alphavirus vectors or plasmid containing the synthetic Gag, Pol, and Env expression cassette; 5) In vivo immunogenicity of recombinant Sindbis replicon vectors containing Gag, Env, and Pol expression cassettes in mice by using intramuscular and subcutaneous routes.
The disclosure further claims that these experiments will exhibit increased potency for induction of cytotoxic T-lymphocytes (CTL) response and humoral immune response by using the Gag, Pol, and Env expression cassettes.

The as-filed specification provides sufficient guidance for one skilled in the art to make an immunogenic composition comprising an expression cassette comprising of a polynucleotide sequence set forth in SEQ ID NOs: 30-32 and make an expression cassette further comprising a viral polypeptide or antigen selected from the group consisting of Gag, Env, vif, vpr, tat, rev, vpu, nef. In addition, the prior art and as-filed specification provide sufficient guidance for one skilled in the art to use the immunogenic composition comprising an expression cassette comprising of one the polynucleotide sequences set forth in SEQ ID NOs; 30-32 in a method of producing an immune response in a mammal by using intramuscular administration.

However, the as-filed specification does not provide sufficient description or one skilled in the art to make a sequence having at least 90% identity to any of the sequences presented as SEQ ID NO: 30-32. The specification does not provide sufficient guidance for what amino acids of any of the sequence listed above may be changed while Pol polypeptide activity is retained. Since the relationship of the sequence of a peptide and its tertiary structure (*e.g.* its activity) are not well understood and are not predictable (Ngo et al. The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), it would require an undue amount of experimentation for one skilled in the art to arrive at other sequences that have at least 90% sequence identity to the Pol polypeptide encoded by SEQ ID NOs: 30-32.

In addition, with respect to the expression cassette further comprising one or more nucleic acid sequences encoding one or more viral polypeptides or antigens, one skilled in the art of making expression cassettes would understand that there is a size limit to the capacity of the cassette being made because one skilled in the art would understand that the functional efficiency of the cassette would be severely limited with several additional nucleic acid sequences (*e.g.* 10 additional nucleic acid sequences). The as-filed specification does not provide sufficient guidance for how many additional polynucleotide sequences can be added to the expression cassette, so the cassette would still function efficiently when introduced into in vitro cells or a mammal. Also, the as-filed specification does not provide sufficient guidance for

what other types of viral polypeptides or antigens (*e.g.* Ebola virus, Dengue virus, etc.) besides HIV polypeptides could be used in the claimed embodiment.

With respect to the claimed invention reading on a cell comprising an expression cassette of claim 1 and its uses. Claims 8-21 read on in vivo/in vitro cells comprising an expression cassette of claim 1. The disclosure does not specifically enable one skilled in the art to determine which cells could be used in *in vitro* and/or *in vivo* methods, since the disclosure does not describe the metes and bounds of the claims. For example, it would be conventional or routine in the art to make and/or use several different cell types (*claims 10-16*) for in vitro production of the HIV Pol polypeptide. However, in light of the specification, one skilled in the art would not envision using the cells in claims 17-21 for in vitro production of the HIV Pol polypeptide. Furthermore, in view of the specification, the only use for claims 17-21 would be for use in a method of ex vivo gene therapy.

In addition, the state of the art and the specification do not provide sufficient guidance for claims encompassing progenitor cells comprising an expression cassette of claim 1. One skilled in the art would understand that if the expression cassette is not stably integrated into the genome of the host cell *e.g.* lymphoid cell, it would not be present after several rounds of replication. Also, one skilled in the art would understand that the development of a successful strategy for long-term gene expression in stem cells is immense (Prince, *Pathology,* Vol. 30, pp. 340, 1998). Prince teaches "the difficulties in determining the conditions to optimize stem cells division and consequently transduction, the ability to recognize and quantify successful transduction into stem cell is problematic (page 340)." Thus, in view of the specification and state of the art, the

specification does not provide sufficient guidance for one skilled in the art to make progenitor cells and stem cells stably transduced with the expression cassette of claim 1.

Furthermore with respect to claims encompassing a method of immunization of a subject using an immunogenic composition comprising the expression cassette comprising an HIV Pol polypeptide encoded by a polynucleotide sequence set forth in SEQ ID NOs: 30-32, the state of the state of the art for immunizing a subject against HIV and in view of the disclosure does not provide sufficient guidance for one skilled in the art to produce a therapeutically effective (partial and/or full protection and treatment) in a subject. The state of the art regarding HIV vaccines as exemplified by Nathanson et al. *The Journal of Infectious Disease*, Vol. 182, pp. 579-89, 2000) suggest that the formulation of an effective AIDS vaccine constitutes a daunting challenge for a number of reasons, including the following:

1) the ability of the virus to persist, to replicate in the face of a vigorous immune response and ultimately, to destroy the integrity of the immune system by an attack on CD4 helper T lymphocytes;
2) the question of whether partial immunity will suffice to protect vaccines against eventual disease;
3) the absence of a single clear-cut immune correlate of protection;
4) the difficulty of inducing neutralizing antibodies;
5) the necessity of defining and inducing CTL epitopes that are immunodominant for each of many different MHC class I haplotypes;
6) the question of whether a vaccine formulated on a virus of a single clade will protect against infection with viruses of other clades;
7) the question of whether an effective vaccine must induce mucosal immunity; and
8) the difficulty of developing an attenuated virus strain is immunogenic (page 586).
Furthermore, Nathanson states that 15 years have past since HIV-1 was isolated and yet the possibility of an AIDS vaccine still appears quite remote (page 579).

In view of the state of the art for producing an HIV vaccine, the as-filed specification does not provide sufficient guidance for one skilled in the art to use the expression cassettes exhibiting the contemplated biological functions as sought in the disclosure (*e.g.* under

conditions that are compatible with expression of said expression cassette) in a method of immunization of a subject. The disclosure does not address what amount of expression of the Pol polypeptide is required in a subject to produce a treatment (encompasses partial/complete protection) and/or prevention (total protection) in said subject. Furthermore, the application does not provide sufficient guidance for how one skilled in the art would circumvent the immunological response of subject for a sufficient time for the Pol polypeptide to be expressed at a sufficient amount to produce a therapeutic response in the subject. This is important because the modulation of the expression level is necessary for each polypeptide to elicit a desired immune response without modifying or shutting the down host cell function and causing negative effects similar to those of traditional vaccines (Azevedo et al., *Brazilian Journal of Medical and Biological Research*, Vol. 32, page 152, 1999). In addition, as-filed specification does not address the concern with repeated administration of an immunogenic vector since repeated administration would cause decrease expression of the desired Pol polypeptide. Also, it would take one skilled in the art an undue amount of experimentation to determine how to target a specific tissue, which requires that the vector avoids degradation in the blood stream and integrates into the desired targeted tissue or cells. In addition, the specification does not provide sufficient guidance for one skilled in the art to determine whether the translation product produced is similar to the native Pol polypeptide encoded by polynucleotide sequences set forth in SEQ ID NOs: 30-32 after the gene is transcribed from the expression cassette in a cell because sometimes proteins are often inactive or otherwise possess different properties from the native protein due to protein folding after expression in a subject's (*e.g.* mice, primate, human, etc.) cells. If the polypeptide produced in the cells is different from the Pol polypeptide set forth in

polynucleotides sequences SEQ ID NOs: 30-32 then the modified polypeptides might not function as indicated by the claimed embodiment (*e.g.* method of immunization of a subject using an immunogenic composition comprising a sequence having at least 90% sequence identity to either SEQ ID NOs: 30-32 into said subject under conditions that are compatible with expression of said expression cassette in said subject).

Furthermore, the examples in the as-filed specification appear to be prophetic examples due to the wording of the each example (*e.g.* verbs are in present tense form). In view of the unpredictability of gene therapy and the doubts expressed in the art of record, one skilled in the art would not be able to reasonably correlate that the examples set forth in the as-filed specification are working examples. In view of these factors (state of the art for gene therapy, skill in the art of producing and HIV vaccine, and prophetic examples) and the concerns listed above, it is not apparent to one skilled in the art how to reasonably extrapolate experiments comprising prophetic examples to any method of immunization of a subject comprising, an immunogenic composition comprising an expression cassette, comprising a polynucleotide sequence encoding a synthetic HIV Pol polypeptide set forth in SEQ ID NOs: 30-32.

In addition to the doubts expressed in Anderson, Nathanson, and Verma, the state of art exemplified by McCluskie et al. (*Molecular Medicine*, 5, pp. 287-300, 1999) teach that "the realization that results in mice often do not predict the situation in humans has also led to a large number of DNA vaccine studies in non-human primates", that "IM injection of plasmid DNA vaccines, while highly immunogenic in mice…was found only to be relatively so in chimpanzees..., and especially not all in Aotus monkeys"' and that "it is probably safe to say that any vaccine that works in a human will work in a mouse, but note necessarily vice-versa" (page

296, column 2, second and third paragraphs). In addition, McCluskie et al. teach that "although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predicative they will be in the case of DNA vaccines where efficacy, by virtue of the requirement first to transfect cells and express the antigen, relies on many factors other than immunological reponses to the antigen" (page 297, column 1).

Thus, it is not apparent as how one skilled in the art reasonably extrapolates, without undue experimentation, from the scope of vertebrate to the full scope of the claimed invention that would generate a treatment (encompasses partial/complete protection) and/or prevention (total protection) in any subject against any subtype of HIV. Even if the specification contemplated that a clear improvement using the synthetic expression cassettes in an immunogenic composition has been prophetically displayed in mice, it is not apparent as to how the prophetic examples are reasonably extrapolated to the full scope of the claimed invention, encompassing any host (*e.g.*, snake, bird, fish, mammal, etc.) particularly given that there is no vaccine generation evidence showing that the prophetic examples are a general phenomenon, and given the doubts expressed in the art of record.

With respect to vaccination methods encompassing routes of administration, e.g., intranasally and intramuscular, the state of the art exemplified by McCluskie teaches that the route of delivery of the DNA vaccine can have an impact on the efficiency of transfection as well as the types and location of cells transfected, and thus potentially on the nature of the immune response (pg. 295). In addition, McCluskie teaches that many different routes have been shown to be effective for DNA delivery in mice; however, few studies have compared responses obtained with

296, column 2, second and third paragraphs). In addition, McCluskie et al. teach that "although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predicative they will be in the case of DNA vaccines where efficacy, by virtue of the requirement first to transfect cells and express the antigen, relies on many factors other than immunological reponses to the antigen" (page 297, column 1).

Thus, it is not apparent as how one skilled in the art reasonably extrapolates, without undue experimentation, from the scope of vertebrate to the full scope of the claimed invention that would generate a treatment (encompasses partial/complete protection) and/or prevention (total protection) in any subject against any subtype of HIV. Even if the specification contemplated that a clear improvement using the synthetic expression cassettes in an immunogenic composition has been prophetically displayed in mice, it is not apparent as to how the prophetic examples are reasonably extrapolated to the full scope of the claimed invention, encompassing any host (*e.g.*, snake, bird, fish, mammal, etc.) particularly given that there is no vaccine generation evidence showing that the prophetic examples are a general phenomenon, and given the doubts expressed in the art of record.

With respect to vaccination methods encompassing routes of administration, e.g., intranasally and intramuscular, the state of the art exemplified by McCluskie teaches that the route of delivery of the DNA vaccine can have an impact on the efficiency of transfection as well as the types and location of cells transfected, and thus potentially on the nature of the immune response (pg. 295). In addition, McCluskie teaches that many different routes have been shown to be effective for DNA delivery in mice; however, few studies have compared responses obtained with

different routes using the same antigen-expressing DNA, dose, and immunization schedule. There have been even fewer studies to compare routes of administration in non-human primates (pg. 295).

At best, the application and the state of the art only provide sufficient guidance for enabling claims directed to for 1) an expression cassette comprising a polynucleotide sequence encoding a Pol polypeptide, wherein the polynucleotide sequence encoding said Pol polypeptide is set forth in SEQ ID NOs: 30-32; 2) The expression cassette of 1, wherein said polynucleotide sequence further comprises a nucleic acid sequence encoding a viral polypeptide selected from Gag, Env, vif, vpr, tat, rev, vpu, nef, and combinations thereof; 3) A composition for generating an immunological response in a mammal, comprising the expression cassette of 1; 4) A method for generating an immune response in a mammal, comprising intramuscularly administrating the expression cassette of 1 to said mammal.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable the claimed invention 1-4, listed above. One would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the application's disclosure, the unpredictability of gene therapy and developing effective HIV vaccines encompassing any subject including any mammal for a protective effect and/or treatment. In addition, the prophetic examples as provided in the specification do not reasonably extrapolate to the full scope of the

claimed invention given that there is no evidence that the prophetic examples are a general phenomenon.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 5, 8, 21, 22, 25, 29, 42, 43, and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The statement in claims 5, 8, 22, 25, and 42 "... **an** expression cassette of claim 1" is indefinite because it does not point out which expression cassette of claim 1. The dependent claim should state "**the** expression cassette of claim 1".

The phrase "comprising an expression cassette of claim .." in claims 22 and 25 renders the claim indefinite. The phrase "comprising an expression cassette of claim .." is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The recitation of the phrase "composition comprising" implies that there has to be an additional element and the claim only describes one element (expression cassette). Clarification is requested.

The phrase "comprising an expression cassette of claim 2" in claim 25 is a relative term which renders the claim indefinite. The phrase "comprising an expression cassette of claim 2" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the

scope of the invention. The claim reads on comprising, which is defined by at least two or more substances. The claim only describes one (expression cassette). Clarification is requested.

The statement in claim 29, "… **a** composition of claim 22" is indefinite because it does not point out which expression cassette of claim 41. The dependent claim should state "**the** composition of claim 22".

The term "tumor-derived" in claim 21 is a relative term, which renders the claim indefinite. The term "tumor-derived" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Thus, since the disclosure does not provide a definition for the term, the metes and bounds of the term are not defined.

The term "HIV-derived" in claim 43 is a relative term, which renders the claim indefinite. The term "HIV-derived" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Thus, since the disclosure does not provide a definition for the term, the metes and bounds of the term are not defined.

The term "derived" in claim 47 is a relative term, which renders the claim indefinite. The term "derived" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Thus, since the disclosure does not provide a definition for the term, the metes and bounds of the term are not defined.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ms. Tracey Johnson whose telephone number is (703) 305-2982.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on M-F, (730-400 EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached at (703) 305-4051.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1633
September 19, 2001

Dave

DAVE T. NGUYEN
PRIMARY EXAMINER